



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,699	02/08/2002	Jingrong Cao	VPI/01-103 US	2092

7590

07/11/2003

Tina Powers
VERTEX PHARMACEUTICALS INC.
130 Waverly Street
Cambridge, MA 02139-4242

EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 07/11/2003

5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
10/071,699

Applicant(s)
Cao et al.

Examiner
Deepak Rao

Art Unit
1624



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jun 9, 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44, 47-51, 54-60, 63, 65, and 67-70 ☒ are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 32-40 ☒ are allowed.
- 6) ☒ Claim(s) 1-31, 41-44, 47-51, 54-60, 63, 65, and 67-70 ☒ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2 6) ☐ Other:

Art Unit: 1624

DETAILED ACTION

Claims 1-44, 47-51, 54-60, 63, 65 and 67-70 are pending in this application.

Election/Restriction

Applicant's election **without** traverse of Group I in Paper No. 4 is acknowledged.

Applicant's election of the species of compound no. III-a-232 (as disclosed in Table 1, page 70) is acknowledged. As the elected species was not found in the prior art, the search was expanded to the genus of the elected invention.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 43-44, 47-51, 54-60, 63, 65 and 67-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of specific types of cancer (e.g., colon cancer), does not reasonably provide enablement for the treatment of most of the other diseases encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Art Unit: 1624

The instant claims are drawn to “a method of inhibiting ERK2 activity” or “a method of treating a disease in a patient” followed by a wide list of diverse disorders. First, the instant claims cover ‘diseases’ that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as kinase inhibitors, useful to treat a laundry list of diseases, which include cancer, inflammatory diseases, autoimmune diseases, neurodegenerative diseases, allergic diseases, etc. Test assays and procedures are provided in the specification in Examples 111-124 related to ERK2, ERK1, GSK-3, AURORA-2, CDK-2, LCK and AKT3 kinase inhibition, wherein the inhibitory activity data for some of the compounds of the invention is provided in Tables 4-5, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders, cancer, viral diseases, infectious diseases, neurological disorders, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite inhibiting the activity of various kinases in a patient, and there is no disclosure regarding how the patient in need of such activity is identified and further, how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement

Art Unit: 1624

requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the laundry list of diseases embraced by the claims having diverse mechanisms or inhibit the recited kinases. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. "There are a number of unanswered questions regarding the role of MAPK in neuronal plasticity and memory formation", see Impey et al., page 14. Also, English et al., express that "The multitude of criteria that must be fulfilled to develop a safe and efficacious drug provide many challenges in targeting MAP kinase pathways". The authors further state that "It remains to be determined if the twin potential of structural information combined with the explosion of genomic information will be powerful enough to surmount the difficulties presented by these enzymes". This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary

Art Unit: 1624

assertion has merits. The existence of such a “silver bullet” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein ‘evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers’. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that “pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles” see page 585, col. 2, lines 33-36.

Further, the list of the diseases includes neurological diseases which covers diverse disorders such as Alzheimer’s disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that “some degenerative diseases are difficult to classify because they involve multiple anatomic locations” (see page 2050). For example, Alzheimer’s disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2,

Art Unit: 1624

wherein it is stated that “[t]here is no cure for Alzheimer’s disease, and no drug tried so far can alter the progress of the disease.” (pg. 1994).

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that “The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.”, see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

Art Unit: 1624

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 41-44, 47-51, 54-60, 63, 65 and 67-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 20, in the definition of Sp, the term "comprising" is open ended and is not permitted in a compound claim. 'Comprising' in a compound claim, leaves the claim open for the inclusion of unspecified groups and/or substituents. The use of the above phrase causes the claim to be broader than the invention. See *In re Fenton*, 451 F.2d 640, 171 USPQ 693 (CCPA 1971). Replacing the term with -- having -- is suggested.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Art Unit: 1624

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-31, 41-43, 47-51, 54-56, 63, 65 and 67-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/121,035 (see the corresponding PG Publication US 2003/0096816). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed compounds overlap reference claimed compounds. The reference teaches pyrimidinyl compound attached to a thienyl group, see formula I in page 61, col. 1. The compounds are also disclosed to be useful as kinase inhibitors, e.g., of Lck type, see page 64, claim 20. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art Unit: 1624

Allowable Subject Matter

Claims 32-40 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds. The closest reference of record, Ejima et al., U.S. Patent No. 6,169,086 does not teach or fairly suggest the instantly claimed compounds having the pyrimidinyl group attached to a substituted pyrrole.

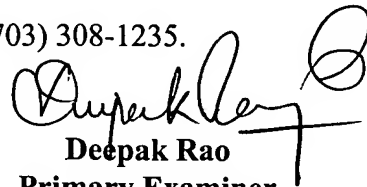
Receipt is acknowledged of the Information Disclosure Statement filed on October 25, 2002 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.


Deepak Rao
Primary Examiner
Art Unit 1624

July 10, 2003